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Dietary potassium and the renal control of salt balance and blood pressure

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Abstract Dietary potassium (K^+) intake has antihypertensive effects, prevents strokes, and improves cardiovascular outcomes. The underlying mechanism for these beneficial effects of high K^+ diets may include vasodilation, enhanced urine flow, reduced renal renin release, and negative sodium (Na^+) balance. Indeed, several studies demonstrate that dietary K^+ intake induces renal Na^+ loss despite elevated plasma aldosterone. This review briefly highlights the epidemiological and experimental evidences for the effects of dietary K^+ on arterial blood pressure. It discusses the pivotal role of the renal distal tubule for the regulation of urinary K^+ and Na^+ excretion and blood pressure and highlights that it depends on the coordinated interaction of different nephron portions, epithelial cell types, and various ion channels, transporters, and ATPases. Moreover, we discuss the relevance of aldosterone and aldosterone-independent factors in mediating the effects of an altered K^+ intake on renal K^+ and Na^+ handling. Particular focus is given to findings suggesting that an aldosterone-independent downregulation of the thiazide-sensitive NaCl cotransporter significantly contributes to the natriuretic and antihypertensive effect of a K^+ -rich diet. Last but not least, we refer to the complex signaling pathways enabling the kidney to adapt its function to the homeostatic needs in response to an altered K^+ intake. Future work will have to further address the underlying cellular and molecular mechanism and to elucidate, among others, how an altered dietary K^+ intake is sensed and how this signal is transmitted to the different epithelial cells lining the distal tubule.

Keywords Potassium · Aldosterone · NaCl cotransporter · Epithelial sodium channel · Renal outer medullary potassium channel

Introduction

Based on observations in hypertensive patients, the Canadian physician W.L.T. Addison suggested already in 1928 that the “prevalence of arterial hypertension (...) is in large part due to potash poor diet, and an excessive use of salt” [3]. Since then, numerous epidemiological, observational, and interventional studies in humans as well as experiments in animals confirmed that not only dietary sodium (Na^+) but also potassium (K^+) intake may have profound effects on blood pressure [1, 61]. In modern societies, the average K^+ intake is usually low (70–80 mmol/day), while the average sodium (Na^+) intake is high (150–200 mmol/day). This contrasts sharply with the diet of our human ancestors who likely ate much more K^+ (230–300 mmol/day) and less Na^+ (1–10 mmol/day) [22, 106]. The change in human eating habits occurred within the last 5,000–10,000 years, when humans started to process their food, which lowered its content of K^+ due to losses during cooking. At the same time, Na^+ intake increased due to artificial salting in order to preserve food and to make it more palatable. In evolutionary terms, 5,000–10,000 years are however rather short and likely not sufficient to adapt our genetic make-up to the new conditions. Therefore, our physiological settings are more prepared for conditions when it was important to conserve Na^+ and to excrete K^+ . The kidneys are the central organs that maintain Na^+ and K^+ homeostasis [106]. They are challenged with the complex task to independently match Na^+ and K^+ excretion to variable dietary intakes and control

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blood pressure at the same time [124]. Healthy kidneys are usually capable to fulfill these tasks. However, the current high Na^+ and low K^+ content in our diet may have shifted the functional capacity of the kidney to its physiological limits. Small imbalances in renal function and/or in the underlying regulatory mechanism are then sufficient to deteriorate the system and thus contribute to the high prevalence of hypertension in our societies. The purpose of this review is (i) to briefly summarize the evidence for the beneficial effect of a K^+ -rich diet on blood pressure and cardiovascular outcome, (ii) to briefly address the cellular and molecular mechanism by which the kidneys control Na^+ and K^+ excretion, and (iii) to highlight recent data providing possible explanations for the beneficial effect of dietary K^+ on renal salt handling and blood pressure control and on how these effects might be mediated at the molecular level.

Effect of dietary K^+ on blood pressure

An impressive body of evidence suggests that dietary K^+ intake is inversely correlated with arterial blood pressure in humans as well as in experimental animals (reviewed in [1, 2, 22, 61, 170]). Although few reports demonstrated that severe K^+ depletion in laboratory animals may decrease blood pressure under certain conditions [7, 46], it is evident from studies in humans that moderate dietary K^+ restriction, as it occurs in our diets, usually increases blood pressure [80, 83]. Conversely, dietary K^+ supplementation was shown to lower arterial blood pressure in humans with essential hypertension [97, 125, 148, 169] and in rat models with spontaneous hypertension [34, 96] or experimentally induced hypertension due to arterial stenosis [167] or dietary Na^+ -loading [32, 105, 168]. While most of these interventional studies were performed with KCl supplementation, it remains controversial whether the antihypertensive effect of a K^+ diet is independent from the accompanying ion [22]. Nevertheless, He and co-workers did not find any differences between KCl and KHCO_3 in their antihypertensive effects [62]. Epidemiological studies have also demonstrated the beneficial effect of dietary K^+ on blood pressure and cardiovascular morbidity and mortality. A strong inverse association between arterial blood pressure and the amount of urinary K^+ excretion, used as surrogate of its dietary intake, has been observed by several investigators [1, 22, 82]. The INTERSALT study did already suggest that urinary K^+ excretion is negatively and independently associated with arterial blood pressure in the general population [71]. However, the number of participants was too small to allow robust subgrouping and a sufficient analysis of the impact of other possibly confounding factors. Very recently, the Prospective Urban Rural Epidemiology (PURE) study included blood pressure recordings, urinary ion excretion values, and other health-relevant parameters from more than

100,000 adults from 18 countries [108]. After adjustment for age, sex, geographic region, body mass index, alcohol consumption, and educational level, the data showed a dominant inverse relationship between systolic blood pressure and urinary K^+ excretion. With each gram increment of urinary K^+ excretion, the associated systolic blood pressure dropped by 1.08 mmHg. Notably, this inverse correlation was seen irrespective from the amount of the urinary Na^+ excretion and hence from the estimated sodium consumption (Fig. 1a). As

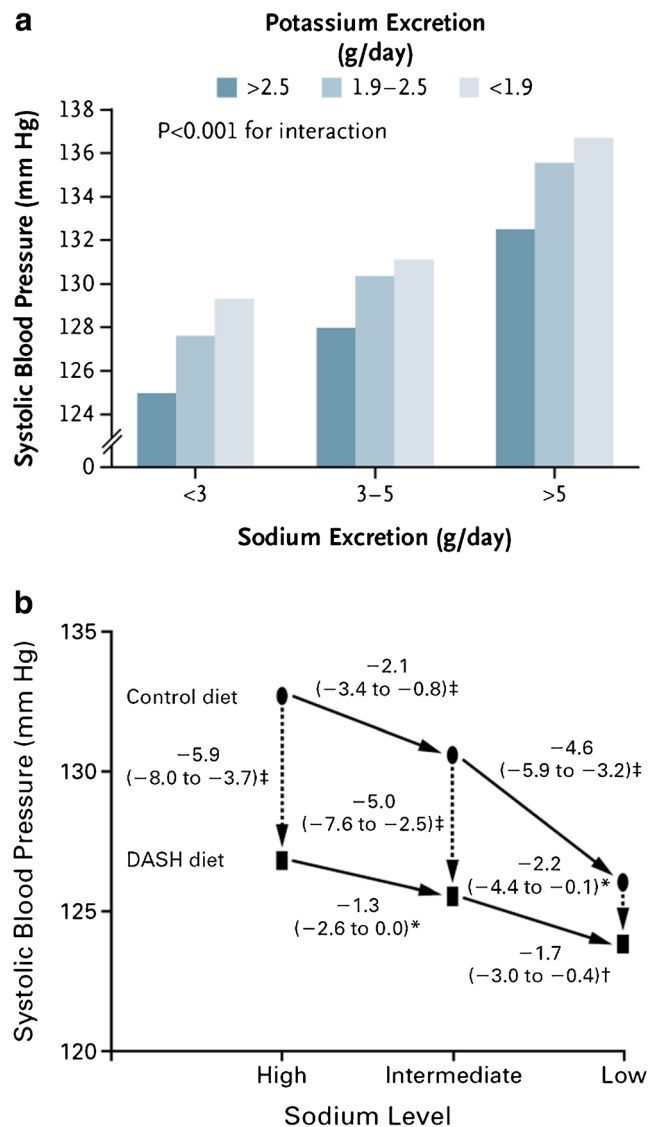


Fig. 1 Effect of dietary Na^+ and K^+ on mean systolic blood pressure in humans. **a** Correlation of 24-h urinary Na^+ and K^+ excretion (as surrogate for ion intake) with systolic blood pressure. Data were collected from 102,216 adults from 18 countries within the PURE study [108]. The *P* value is for testing the joint effect of the two electrolytes on blood pressure (from [108]). **b** Effects of Na^+ and K^+ dietary intake on the mean systolic blood pressure. The study included 412 participants which were randomly assigned to eat either a control diet or the fruit- and vegetable-rich DASH diet. Within the assigned diet, participants ate foods with either high, intermediate, or low levels of sodium for 30 consecutive days (from [148])

such, these data from an observational study are in line with data from the interventional Dietary Approach to Stop Hypertension (DASH) trial [148]. The DASH diet is rich in vegetables and fruits and part of its blood pressure-lowering effect can likely be attributed to its high K^+ content. Irrespective whether this diet was combined with a high, intermediate, or low dietary Na^+ intake, it significantly reduced blood pressure. Nevertheless, the effect was more pronounced on the high than on the low Na^+ intake (Fig. 1b). Importantly, a high K^+ diet does not only lower blood pressure but does also decrease the risk for its complications including cardiovascular events, stroke, and death [2, 116]. In general, persons especially vulnerable to these complications (e.g., obese persons, older persons, or patients with hypertension) appear to profit most from the beneficial effects of a K^+ -rich diet [108]. In contrast to the pronounced effects seen in hypertensive patients, a high K^+ intake does not or only minimally decrease blood pressure of normotensive humans and animals [12, 61, 170]. These evidences suggest that dietary K^+ interferes with the regulation of blood pressure only when the balance in regulatory mechanisms is disturbed. Moreover, there might be an optimal level of K^+ intake up to which the blood pressure-lowering effect could be achieved. Indeed, experiments in Dahl salt-resistant and salt-sensitive rats on a Na^+ replete diet showed that the antihypertensive effect of K^+ supplementation occurred only with 2.6 % KCl. Treating the animals with an excessive and unphysiological high K^+ intake (4 and 8 % KCl) triggered a progressive rise in blood pressure to levels even higher than those observed in rats on low K^+ (0.7 % KCl) intake [100]. As the increase in blood pressure was paralleled by elevated plasma aldosterone levels, it was suggested that aldosterone-dependent Na^+ retention could explain the hypertension. However, the inhibition of the mineralocorticoid receptor by spironolactone was not able to prevent the hypertensive effect of an excessive K^+ intake in mice [182].

The underlying mechanisms for the beneficial effect of a physiologically relevant high K^+ diet on blood pressure and the cardiovascular system have been addressed in many research studies (reviewed in [22, 170]). They were proposed to include direct effects of altered plasma K^+ levels on endothelial cells leading to reduced endothelial stiffness and enhanced nitric oxide (NO)-mediated vasodilation [118], endothelial and vascular smooth muscle cell hyperpolarization and relaxation [22], an altered response of arterial baroreceptors [149], a lowered sympathetic activity [52], a reduced renal renin release [12], and a general negative sodium balance [70]. The latter is particularly interesting, given the fact that an enhanced dietary K^+ intake stimulates adrenal aldosterone production, which is expected to promote Na^+ retention rather than to give rise for a Na^+ loss. However, numerous experimental studies in sheep [134, 135], dog [205], rat [179], mouse [156], and human [79, 176] convincingly showed that a K^+ load is followed not only by a sustained kaliuresis but

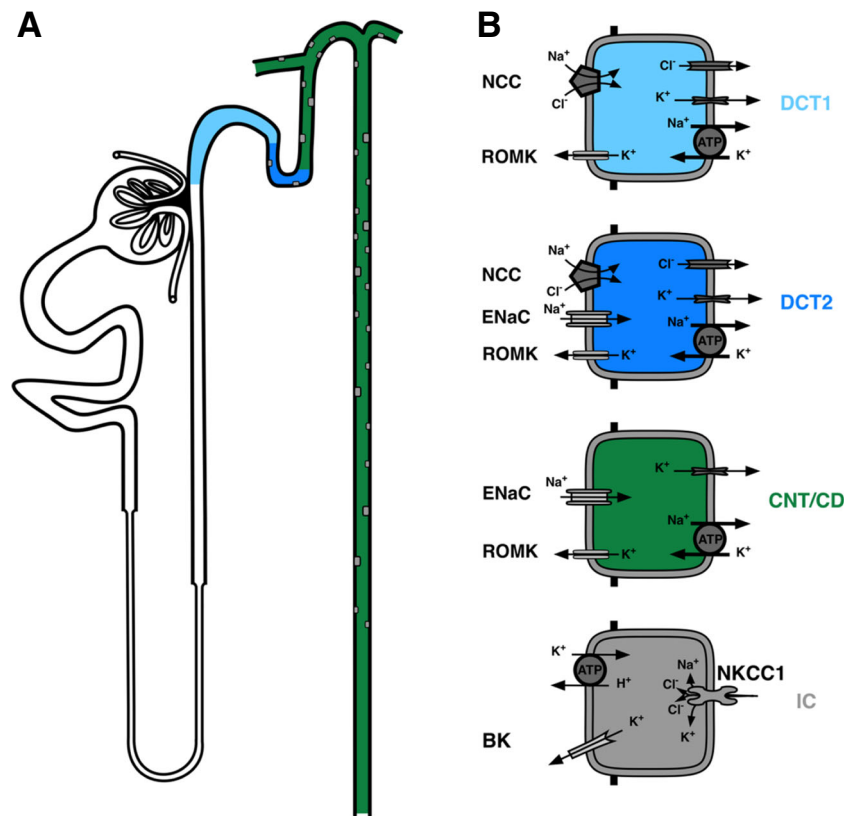
also by a pronounced natriuresis. While the first parallels the enhanced K^+ intake, the latter usually exceeds the intake of Na^+ explaining the negative Na^+ balance. The experiments in sheep [134] and mice [156] showed that the K^+ -induced natriuresis starts very rapidly and in parallel to the increasing urinary K^+ excretion. The natriuresis occurs independently whether the K^+ was given with the food or administered by infusion [134, 135, 170]. Notably, the K^+ -dependent inhibition of renal Na^+ reabsorption is accompanied by an enhanced chloride excretion [171, 176] suggesting a combined renal NaCl loss. Thus, there is a close interrelationship between renal K^+ and Na^+ handling that likely also impacts on renal blood pressure control.

Role of the distal tubule in the control of K^+ and Na^+ balance and blood pressure

K^+ and Na^+ are freely filtered at the glomerulus and then reabsorbed to almost 90 % along the proximal tubule (PT) and the thick ascending limb (TAL) [124, 136]. Thus, only ~10 % of the filtered Na^+ and K^+ load reach the distal tubule segments beyond the macula densa. However, these post-macula densa segments, which include the distal convoluted tubule (DCT), the connecting tubule (CNT), and the collecting duct (CD) with its cortical (CCD) and medullary (MCD) portion, are decisive for the amount of Na^+ and K^+ that gets finally excreted via the urine [92, 106, 124, 136]. The molecular identification of the major ion transporters and channels of the distal tubule enabled researchers to map these proteins along the DCT, CNT, and CD and to study their function at the molecular level as reviewed in detail recently [5, 30, 142]. Despite some subtle species differences, the cellular distribution and sequential order of the ion-transporting and regulating proteins appear to be strikingly similar in all yet investigated mammalian species (reviewed in [91]). The segmentation of the nephron and the various cell types of the distal tubule including their main Na^+ and K^+ transporting pathways are schematically depicted in Fig. 2.

In the initial 2/3 of the DCT (DCT1), the apical thiazide-sensitive NaCl cotransporter (NCC) is almost the sole apical Na^+ transport pathway. In the last 1/3 of the DCT (DCT2), NCC is co-expressed with the amiloride-sensitive epithelial sodium channel (ENaC) [6, 91, 106]. ENaC is composed of three homologous subunits (α , β , and γ ENaC) and is the main apical sodium-reabsorbing pathway in the CNT and CD [92]. In contrast to NCC, the activity of ENaC is electrogenic and generates a transepithelial potential difference that is crucial to drive K^+ secretion via apical K^+ channels [18, 29]. K^+ secretion is accomplished by the renal outer medullary K^+ channel in the segment-specific principal cells of the DCT, CNT, and CD [189, 192]. Interspersed between the segment-specific cells are the intercalated cells, which are abundant from

Fig. 2 **a** Schematic representation of a nephron. Highlighted with color is the distal nephron including the distal convoluted tubule (DCT) with an early and late portion (DCT1 and DCT2, respectively), the connecting tubule (CNT), and the collecting duct (CD). The gray rectangles indicate the distribution of intercalated cells (IC). **b** Schematic cell models with representation of the main apical and basolateral transport pathways contributing to Na^+ reabsorption and K^+ secretion in the respective tubule segment. Abbreviations for the ion channels, transporters, and ATPases are explained in the text



DCT2 to the first portion of the MCD. Intercalated cells contribute to renal K^+ secretion via apical Ca^{2+} -dependent-maxi K channels (BK) [64, 122]. BK channels are supposed to mediate the flow-dependent K^+ secretion in the distal tubule and collecting duct [198]. BK is composed of a pore-forming α -subunit and a modulatory β -subunit, for which four distinct forms ($\beta 1$ –4) with tissue-specific expression have been described [199].

The intercalated cells do also express an apical H^+ - K^+ -ATPase that can reabsorb K^+ from the tubular fluid in exchange for protons [31, 57]. As such, the intercalated cells are capable for both K^+ secretion and K^+ reabsorption and likely contribute to the ability of the DCT, CNT, and CD to switch from K^+ secretion during a high K^+ intake to K^+ reabsorption during dietary K^+ restriction [159]. Certain types of intercalated cells do also express an apical $\text{Cl}^-/\text{HCO}_3^-$ exchanger (pendrin) and a Na^+ -driven chloride/bicarbonate exchanger (NDCBE), which were proposed to contribute to transcellular NaCl reabsorption along the renal collecting system [37, 187]. Indeed, there is ample evidence for an important crosstalk and cooperation between the segment-specific cells and intercalated cells and their ion transport pathways in order to maintain Na^+ and K^+ homeostasis as well as a normal blood pressure [37, 64, 194]. In the segment-specific cells of the DCT, CNT, and CD, Na^+ reabsorption and K^+ secretion are driven by the activity of the Na-K-ATPase in the basolateral plasma membrane. By pumping Na^+ towards the extracellular space and

K^+ in the opposite direction, it keeps the intracellular Na^+ concentration low and the intracellular K^+ concentration high, thereby providing the necessary ion gradients for the ion fluxes across the apical membrane [194]. However, the intercalated cells express very little of the Na-K-ATPase [17], and it remains unclear how these cells contribute to significant Na^+ reabsorption and K^+ secretion. It was recently postulated that intercalated cells may rely on a H^+ gradient generated by the H^+ vacuolar-ATPase as bioenergizer for secondary active transport [23]. Moreover, immunohistochemical studies revealed that the intercalated cells have a prominent abundance of the Na-K-2Cl transporter NKCC1 in their basolateral plasma membrane, which was proposed to ensure a sufficient basolateral K^+ uptake to fuel K^+ secretion via apical BK channels [89].

The functional relevance of the DCT, CNT, and CD for the control of Na^+ and K^+ homeostasis as well as blood pressure is evidenced by human monogenic diseases affecting ion transport in these three segments (reviewed in, e.g., [142, 193]). Loss-of-function mutations of NCC cause Gitelman's syndrome which is characterized by renal Na^+ loss with arterial hypotension, hypokalemic alkalosis, and hypocalciuria [76, 87, 155]. Conversely, increased NCC activity due to mutations within the regulatory network including the With-No-lysine (K) WNK kinases WNK1 or WNK4 [196] or ubiquitin-ligase co-factors cullin-3 (CUL3) [14] and kelch-like 3 protein (KLH3) [14, 95] is associated with severe salt-sensitive

hypertension, hyperkalemia, metabolic acidosis, and hypercalciuria (familial hyperkalemic hypertension (FHHt), Gordon syndrome, or pseudohypoaldosteronism type II). Likewise, loss-of-function mutations in ENaC cause severe renal salt-wasting with often life-threatening hyperkalemia and acidosis (pseudohypoaldosteronism type I) [24, 161], while gain-of-function mutations of ENaC (Liddle syndrome) are associated with salt-sensitive arterial hypertension with hypokalemic alkalosis [59, 60, 153]. Remarkably, although these diseases primarily affect Na^+ transporting pathways, they also affect renal K^+ handling and in part also renal Ca^{++} , Mg^{++} , and acid/base excretion, further emphasizing the important interrelation of these ion transport processes in the distal tubule. Transgenic mouse models for Gitelman syndrome [151], FHHt [81, 166, 203], PHA-I [11, 68, 103], and Liddle syndrome [132] have been generated and mimic to a large extent the human diseases. This review will not discuss these models but briefly highlight only those mouse models with deletion for K^+ -transporting proteins for which corresponding human diseases have not been described or for which the mouse models show relevant differences from the human phenotype.

Knockout mouse models for the apical secretory potassium channels ROMK [94, 185] and BK [16, 131, 150] as well as for the gastric and colonic isoform of the H-K-ATPase [107, 157] have been developed. The phenotype of the ROMK-deficient mice is dominated by the transport defect in the thick ascending limb. Here, ROMK-dependent K^+ secretion is important to provide a sufficient intratubular K^+ concentration to ensure the activity of the apical furosemide-sensitive Na-K-2Cl cotransporter NKCC2. Consistent with a loss of NKCC2-dependent Na^+ reabsorption, the mice show a severe Bartter-like syndrome with a high perinatal lethality and poor urinary concentration ability. In contrast to patients with Bartter syndrome, the ROMK-deficient mice do not show hypokalemic alkalosis but metabolic acidosis likely resulting from the severe polyuria with subsequent hydronephrosis and renal insufficiency [94]. As such, these mice could not be used to study the role of ROMK for renal K^+ secretion in the DCT, CNT, and CD. However, the observation that infants with Bartter syndrome due to ROMK mutations are usually hyperkalemic and not hypokalemic as patients with mutations in other Bartter syndrome-related genes (i.e., NKCC2, CIC-K, barttin, and the calcium-sensing receptor) [72] point to the relevance of ROMK for renal K^+ excretion.

The role of BK channels for renal K^+ excretion and blood pressure control has been studied using knockout mouse models for its subunits [64]. BK α -deficient mice featured an impaired flow-dependent urinary K^+ secretion and hyperaldosteronism probably to compensate for the disturbed renal K^+ secretion [138]. Likewise deletions of the ancillary BK β 1 and BK β 4 subunits results in insufficient renal K^+ excretion, hyperaldosteronism, and arterial hypertension [56, 63]. However, the effect of BK β 1 deletion on aldosterone

release and blood pressure critically depends on the genetic background of the mice and the physiological role of this subunit remains elusive [147]. The experiments in ROMK-deficient and in BK-deficient mice did also reveal that both channels may compensate for each other [8, 138]. This may explain the rather mild defect in renal K^+ excretion observed in these mice.

Other putative players in the renal handling of K^+ are the gastric (HK α 1) and colonic (HK α 2) isoforms of the H^+ - K^+ -ATPase. Renal H^+ - K^+ -ATPases are expressed throughout the kidney, and their expression is profoundly upregulated by dietary K^+ restriction, suggesting that they may contribute to renal K^+ homeostasis [31, 57]. Besides the clear deficits in gastric and colonic functions displayed by H^+ - K^+ -ATPase knockout mice (including gastric achlorhydria and epithelial metaplasia (HK α 1 knockout mice) [157] and insufficient colonic K^+ reabsorption under dietary K^+ restriction (HK α 2 knockout mice) [107]), no overt renal phenotype has been reported so far. Further studies are warranted to elucidate their role in renal physiology as detailed in two recent review articles [31, 57].

Effect of K^+ intake on K^+ and Na^+ transport in distal tubules

The vast majority (~98 %) of the K^+ content of the body (~3,500 mmol) is stored inside the cells. Only a small amount of K^+ (70–100 mmol) is found in the extracellular space. Thus, the standard daily K^+ intake of humans (~100 mmol) just equals the amount of extracellular K^+ [55]. In smaller mammals, like the mouse, the standard daily K^+ intake may even exceed the amount of extracellular K^+ up to a factor of 40 [156]. The fact that under these conditions, a single meal does not cause a life-threatening increase of the extracellular K^+ concentration is mainly due to (i) a rapid shift of extracellular K^+ into intracellular stores (internal K^+ balance) and (ii) a rapid onset of K^+ excretion via the kidney and to less extent also via the colon (external K^+ balance) [119]. In the kidney, the increase in urinary K^+ excretion is achieved via an activation of both apical K^+ channels and Na^+ channels, as well as the basolateral Na^+ - K^+ -ATPase [189]. Electrophysiological data on isolated collecting ducts demonstrated that an enhanced dietary K^+ intake increases the number of active K^+ and Na^+ channels in the apical membrane rather than changes the open probability and/or conductance of single channels [120, 121]. Immunofluorescence studies and/or in vivo cell surface biotinylation assays corroborated these findings and showed that the increase in the number of active channels is due to a translocation of BK [112], ROMK [50, 173, 183], and ENaC [50, 173] from intracellular pools to the apical plasma membrane. The activation of ROMK and ENaC in response to dietary K^+ loading occurs quite rapid and was suggested to

contribute to the renal adaptation to day-to-day variations in dietary K^+ intake [121]. The K^+ diet-induced activation of BK is paralleled by an enhanced mRNA expression of the BK α and BK β 2-4 subunits [112] and BK α protein abundance [90, 138]. The latter is possibly related to a reduced ERK1/2 signaling-mediated lysosomal degradation of the channel [90]. In contrast, the activation of ROMK is not associated with an increased ROMK transcription [51] but goes along with an enhanced abundance of its fully glycosylated form suggesting an increased processing of ROMK through the Golgi apparatus [50]. ENaC does also undergo post-translational modification. The K^+ diet-induced activation of ENaC is accompanied by a proteolytic cleavage of the α - and γ ENaC subunits and a shift of β ENaC to higher molecular weight forms consistent with an altered glycosylation pattern [50]. While the significance of the latter is unclear, the proteolytic cleavage of α - and γ ENaC is thought to represent the activation of otherwise silent channels [143]. It is important to note that, in contrast to ENaC [47, 102], the K^+ channels BK [40] and ROMK [120] do not get activated in response to dietary Na^+ restriction, suggesting that increased plasma aldosterone levels are per se not sufficient to bring the K^+ channels to the apical plasma membrane. The differential regulation of ENaC and ROMK in response to dietary Na^+ restriction and K^+ loading (Fig. 3) may contribute to the ability of the kidney to independently regulate Na^+ and K^+ homeostasis. Notably, the apical translocation of ROMK [183] and ENaC [106, 173] in response to dietary K^+ loading occurs mainly in the late DCT (DCT2) and early CNT. These findings are in line with early micropuncture studies suggesting that renal K^+ excretion

is mainly achieved at these sites [99]. Consistent with a high K^+ transport capacity, the late DCT and early CNT are characterized by a high density of the Na-K-ATPase and of mitochondria (reviewed in [106]). The activity of ENaC in these segments is much more pronounced than in the downstream localized CD [48, 114]. The critical role of the late DCT and CNT for maintenance of K^+ and Na^+ homeostasis has been extensively discussed in several recent reviews [92, 106, 123] and is underlined by the fact that mice with targeted inactivation of ENaC in the CCD are phenotypically normal [145], while mice with targeted inactivation of ENaC in the CNT show an impaired control of K^+ and Na^+ homeostasis [29].

Although recent experiments in rats suggested that part of the K^+ secretion in response to a dietary K^+ load occurs independent from ENaC [49], the upregulation of this electrogenic Na^+ reabsorption certainly supports renal K^+ secretion. As mentioned earlier in this review, the activity of ENaC is necessary to generate a transepithelial potential difference that drives K^+ apical secretion [18, 29]. However, the increased Na^+ reabsorption in the distal tubule is at odds with the described natriuretic and antihypertensive effect of a K^+ -rich diet. A possible explanation for this apparent paradox comes from recent observations on the effect of dietary K^+ intake on the activity of NCC in the DCT [156]. An oral K^+ load by gastric gavage or feeding rapidly (<15 min) dephosphorylates and hence inactivates the thiazide-sensitive NaCl cotransporter NCC. This response parallels the K^+ -induced kaliuresis and natriuresis (Fig. 4) and precedes a detectable activation of ENaC by proteolytic cleavage [156]. The K^+ diet-induced NCC downregulation is also seen under chronic

Fig. 3 Effect of dietary K^+ loading and dietary Na^+ restriction on the subcellular localization of ROMK and γ ENaC in mouse CNTs. Mice were kept either for 1 week on a control diet (0.8 % K^+ , 0.3 % Na^+), for 2 days on a high K^+ diet (3 % K^+ , 0.3 % Na^+), or for 10 days on a low Na^+ (0.8 % K^+ , 0.01 % Na^+). Immunohistochemical detection of ROMK (in green) and γ ENaC (in red)

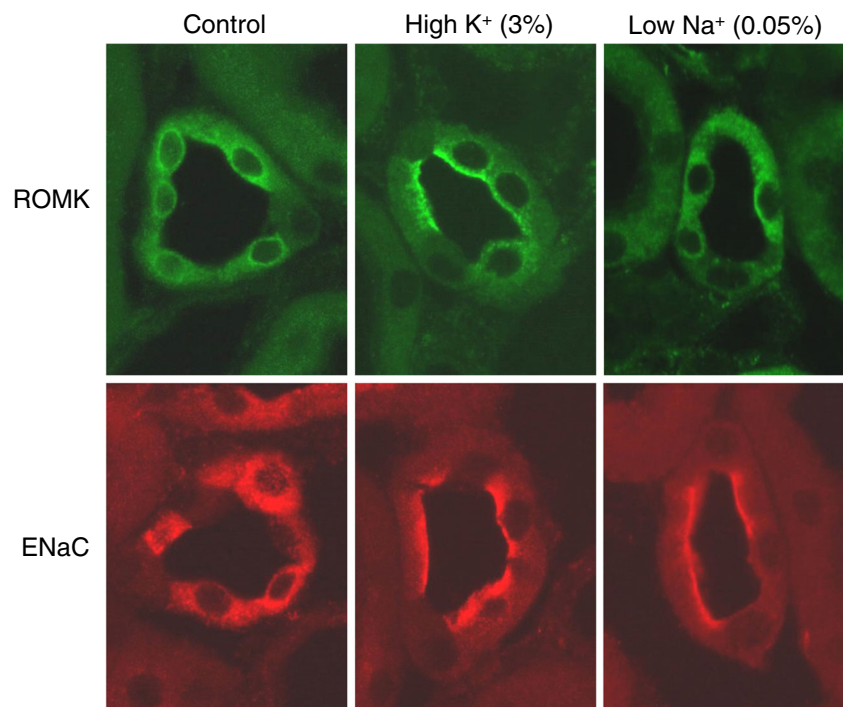
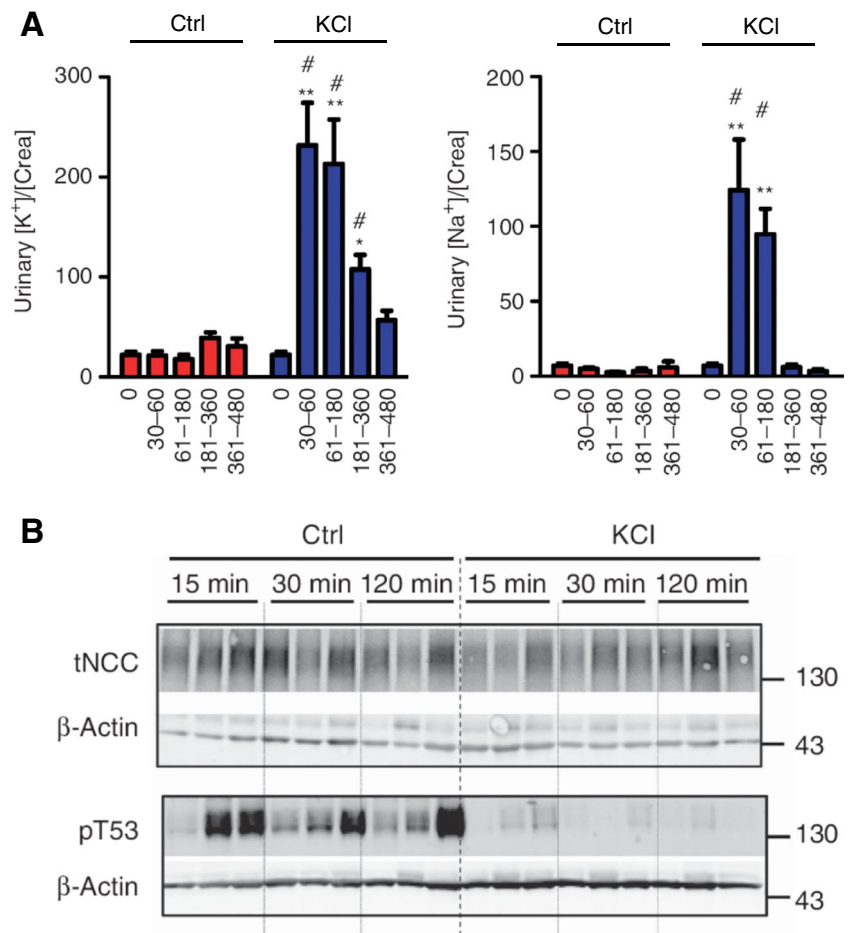


Fig. 4 Rapid effects of an oral K^+ load on urinary ion excretion and NCC phosphorylation. **a** Urine K^+ and Na^+ concentrations normalized to creatinine concentrations from mice after receiving a gastric gavage of control (*Ctrl*; red; 0 % KCl) or KCl (*blue*; 2 % KCl) solutions. Spot urines were collected for the indicated time intervals after gavage. * $P<0.05$ and ** $P<0.01$ between *Ctrl* and experimental groups. # $P<0.05$ between the “zero” and the time intervals within the same experimental group. **b** Male mice received control (*Ctrl*) and 2 % KCl solutions through gavage, and kidneys were collected after 15, 30, and 120 min. Total NCC (*tNCC*) and phosphorylation of NCC at position 53 (*pT53*) were assessed by immunoblotting with specific antibodies. Error bars indicate standard error of the mean. (Graphs and immunoblots from [156])



conditions (i.e., days to weeks of a high K^+ diet) but concerns mainly the total and cell surface-expressed NCC rather than its phosphorylation [50, 73, 179, 182, 200]. Moreover, while the acute effect on NCC appears to be independent from the co-administered anion [156], the chronic effect on NCC abundance and phosphorylation was reported to occur only when the K^+ is accompanied by chloride and not by citrate [20]. Notably, the downregulatory effect of a high K^+ diet is independent from dietary Na^+ intake and is seen on standard Na^+ [50, 175], high Na^+ [182], and low Na^+ intake [179]. These findings are in agreement with early renal tubule micropuncture studies on rats showing a diminished natriuretic response to thiazides after dietary K^+ loading [154]. Previous morphological studies had already revealed a reduced density of mitochondria and basolateral membrane infoldings in DCTs of rabbits on a low Na^+ /high K^+ intake [75].

The downregulation of NCC in response to a high K^+ diet was proposed to improve the secretion of K^+ in DCT2, CNT, and CD due to the increased apical Na^+ and fluid delivery [5, 104]. Na^+ can be then reabsorbed in exchange for K^+ while the enhanced urinary flow may activate flow-dependent K^+ secretion and lower intratubular K^+ , keeping the driving force for K^+ secretion high [192]. Nevertheless, it is unlikely that a

reduced activity of NCC is sufficient to increase urinary K^+ excretion unless a sufficient number of active K^+ and Na^+ channels is present at the apical plasma membrane [26, 69]. However, given that thiazide diuretics [39] significantly lower blood pressure, it is reasonable to assume that the observed NCC downregulation in K^+ -repleted animals is sufficient to contribute to the antihypertensive effect of a high K^+ diet. On the other hand, an upregulation of NCC may increase blood pressure on a low K^+ intake. In fact, studies in rats and mice demonstrated that dietary K^+ restriction increases the abundance and phosphorylation of NCC [38] leading to renal Na^+ retention and an elevated blood pressure [182]. However, it is unlikely that the effects of an altered dietary K^+ intake on renal Na^+ excretion and blood pressure control can be solely attributed to an altered NCC activity. In fact, although the K^+ -induced natriuresis in NCC-deficient mice is diminished, they still excrete more Na^+ than NCC-deficient mice without any K^+ loading [156]. The nature of the remaining K^+ -induced natriuresis in NCC-deficient mice is unclear but might be related to inhibitory effects of K^+ loading on Na^+ transport in the proximal tubule [15] and in the TAL [26, 78, 160, 164]. Consistently, an altered K^+ intake may modulate also the expression of ion transporters in the proximal tubule and the

TAL including NHE3 and NKCC2 as shown in some [38, 47, 73] but not all studies [115].

The role of aldosterone

Aldosterone is regarded as the main hormone mediating the effects of K^+ intake on the kidney while also regulating Na^+ balance and contributing to blood pressure control. A high dietary K^+ intake increases plasma $[K^+]$, which promotes aldosterone production and release from the zona glomerulosa of the adrenal cortex [10]. The elevated plasma aldosterone levels are then thought to stimulate renal K^+ secretion until the excess of K^+ is excreted [55]. Indeed, aldosterone is known to stimulate K^+ secretion in the renal collecting system, and several evidences suggest that it may interfere with the regulation of most of the molecular players involved in distal tubule K^+ transport including ENaC [92], ROMK [186], BK [195], and NCC [77, 177, 178]. However, the effects of physiological elevations of plasma aldosterone on renal K^+ excretion are rather minor and a dietary K^+ load induces a kaliuresis often already before plasma aldosterone levels get elevated [133]. Moreover, adrenalectomized animals are able to adapt their urinary K^+ excretion and to increase apical Na^+ and K^+ conductances in the CD in response to a dietary K^+ load [120, 158, 197]. Likewise, mice with a genetic inactivation of the aldosterone synthase maintain an adequate renal adaptation to a physiological K^+ load (2 % K^+ diet). Only when challenged with an unphysiological high (5 %) K^+ diet, the aldosterone synthase-deficient mice decompensate and become severely hyperkalemic likely due to an insufficient upregulation of ENaC rather than of ROMK [173]. The independence of ROMK and BK activity from aldosterone could be also deduced from the fact that these channels do not get activated upon Na^+ dietary restriction, despite the elevated plasma aldosterone levels [40, 120, 121]. Moreover, aldosterone does not increase K^+ channel activity in a mouse CCD cell line [45]. It was also shown that the K^+ diet-induced downregulation of NCC is aldosterone-independent [156].

Thus, there is ample evidence that in addition to aldosterone, aldosterone-independent factors contribute to the renal control of K^+ homeostasis. A variety of additional hormones were implicated in the regulation of renal K^+ secretion, and many of them do also control Na^+ balance and blood pressure. Indeed, glucocorticoids [43] and vasopressin [19, 44] stimulate renal K^+ secretion. Part of their effect might be related to their known activating effects on ENaC. Moreover, glucocorticoids increase urinary flow and thereby may activate flow-dependent K^+ secretion [43], while vasopressin was reported to directly activate ROMK [19]. Conversely, progesterone gets increased during hypokalemia and was shown to stimulate renal K^+ reabsorption via an increased $H^+-K^+-ATPase$ activity in the kidney [31, 36]. Angiotensin II suppresses the

activity of BK [211] and ROMK [191, 207] but stimulates ENaC [165, 188] and NCC [21, 85, 177] and hence might be critical to limit renal K^+ secretion and to maximize renal Na^+ reabsorption during hypovolemia [5]. Nevertheless, although all of the abovementioned hormones likely contribute to the modulation of the K^+ response of the kidney, their described physiological effects on renal K^+ handling are comparably small and unlikely account for the marked aldosterone-independent regulations of, for example, ROMK and NCC in response to a high K^+ diet.

The existence of additional humoral kaliuretic factors has been proposed since more than 25 years [146]. Although there are evidences for the presence of such factors in blood [33] and urine [98] of K^+ -loaded animals, their molecular identity remains unclear. It has been proposed that the amount of dietary K^+ is already sensed in the gut and/or the portal vein even before plasma K^+ levels rise [55]. This would trigger the release of kaliuretic peptides and/or modulate the activity of the autonomous nervous system ultimately increasing renal K^+ excretion [55]. Similar feed-forward control systems involving gut-derived peptides have been implicated in the control of glucose and Na^+ homeostasis [109]. Although previous data suggested a gut-kidney crosstalk for the control of K^+ homeostasis [86], additional work is needed to further substantiate this concept.

Changes in extracellular K^+ concentrations may also directly affect renal ion transport. There is strong evidence that increases in plasma K^+ are already sufficient to stimulate renal K^+ and Na^+ excretion [180], to increase the apical K^+ conductance in distal tubules [43, 197], and to downregulate NCC in the DCT [137]. K^+ infusions into one renal artery of dogs induce a prominent kaliuresis and natriuresis in the ipsilateral kidney, while the contralateral kidney shows only mild kaliuresis and no natriuresis [180]. One possible intrarenal mediator could be tissue kallikrein (TK), which is a serine protease synthesized in large quantities in the late DCT and CNT [181]. TK synthesis and excretion into the urine is increased by dietary K^+ intake [181], and it activates ENaC by proteolytic cleavage [126]. Nevertheless, the defect in renal adaptation to a K^+ load displayed by TK-deficient mice is rather subtle [35], and the proteolytic cleavage of ENaC in TK-deficient mice is only marginally changed [129].

Thus, there is a large body of experimental evidence suggesting that aldosterone-dependent and aldosterone-independent mechanisms contribute to the renal response to a high K^+ intake. Aldosterone is certainly not an absolute prerequisite [192], but it is important to achieve a maximal K^+ secretion [101, 173]. Moreover, aldosterone may have an important additional role. The aldosterone-dependent upregulation of ENaC in the late DCT, CNT, and CD may not only improve K^+ secretion but may also limit the renal Na^+ loss caused by the inactivation of upstream Na^+ transport systems. As such, the increase of plasma aldosterone would contribute

to maintain Na^+ balance and hence finally blood pressure on high K^+ diet. The relevance of an intact aldosterone system in this context is highlighted by experiments performed by Young and co-workers in dogs [205]. While intact dogs showed only a limited natriuresis and no significant change in blood pressure in response to a K^+ load, adrenalectomized dogs with a fixed corticosteroid and aldosterone replacement revealed a profound K^+ intake-induced renal Na^+ loss with a marked drop in arterial blood pressure (Fig. 5). Thus, the K^+ sensitivity of blood pressure may become overt only when underlying feedback mechanisms of blood pressure control are disturbed. This may also explain the observation that a high K^+ diet has a marked blood pressure-lowering effect only in hypertensive but not in normotensive individuals (see above).

The role of SGK1 and the WNK/SPAK pathway

In recent years, tremendous progress has been made in the identification and characterization of molecular mechanisms

that regulate the ion transporters and channels involved in renal Na^+ and K^+ handling in the DCT, CNT, and CD. This research was summarized in several recent reviews [4, 54, 127, 162, 174, 192]. In brief, the current evidence suggests that the regulation of Na^+ and K^+ transport in the post-macula densa segments depends on an intricate regulatory network that includes the interaction of several kinases (e.g., WNK1, 3, and 4, SPAK/OSR1, SGK1) [4, 54, 65], phosphatases, and their regulators (e.g., PP1, PP4, I-1) [53, 88, 130] as well as ubiquitin ligases (e.g., Nedd4-2, KLHL-3, cullin-3) [141, 174]. In the context of the renal adaptation to an altered dietary K^+ intake, the kinases SGK1, WNK1, and WNK4 receive particular attention. SGK1 was proposed to mediate the aldosterone-dependent effects of a high K^+ diet [192]. In fact, aldosterone [27, 113] and a high K^+ intake [204] induce the expression of SGK1. Moreover, SGK1 increases the cell surface abundance and/or activity of apical and basolateral players contributing to K^+ secretion including ROMK [204, 207], BK [208], ENaC [93], and the Na-K-ATPase [209]. Consistent with the idea that SGK1 takes part in the renal adaptation to a high K^+ intake, SGK1-deficient mice show an

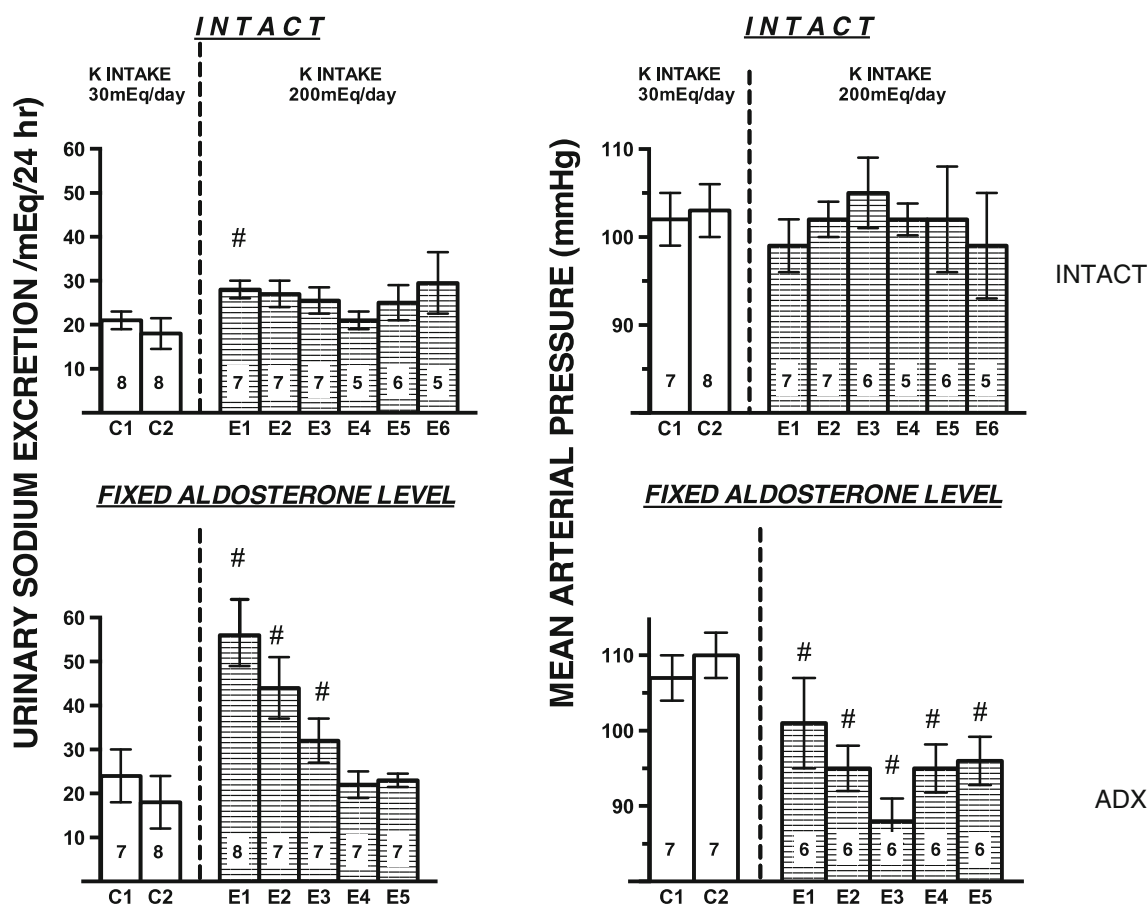


Fig. 5 Intact dogs (*n* indicated in the bars) were kept for 2 days (C1–C2) in metabolic cages with a control diet in which the K^+ intake was fixed to 30 mEq/day. After the second control day, additional 170 mEq/ KCl (total 200 mEq/day) was administered by a venous catheter connected to a pump for the next 6 days (E1–E6). After this set of experiments, the dogs

were adrenalectomized (ADX) and supplemented with 50 $\mu\text{g/day}$ of aldosterone, and the experiment was repeated. In both experimental setups, urinary Na^+ and mean arterial pressure were measured. Hashtags indicate statistical significance between the given measurement and C2. Error bars indicate standard error of the mean. (Redrawn from [205])

impaired renal K^+ excretion and become hyperkalemic when placed on a high K^+ diet [67]. However, the underlying molecular mechanisms are likely complex. In contrast to what was expected, SGK1-deficient mice do not show a reduced but rather an increased apical localization of ROMK [67]. Moreover, the effect of the loss of SGK1 on apical ENaC activity is inconsistent. While an early study [200] reported a reduced activity of ENaC in kidneys of SGK1 knockout mice, a later study in a different mouse model [42] reported unchanged apical ENaC activity. Interestingly, SGK1-deficient mice reveal a reduced NCC abundance and phosphorylation that drops even more during dietary K^+ loading [175] and Na^+ restriction [41]. The downregulation of NCC under standard conditions could be explained by the loss of the stimulatory action of SGK1 on NCC [144], but the further decrease of NCC on high K^+ or low Na^+ diet is apparently SGK1-independent and perhaps secondary to the developing hyperkalemia in these mice [41, 175]. Thus, SGK1 likely contributes to the renal control of K^+ balance, but there is certainly a high degree of redundancy in the underlying signaling pathways.

In these, WNK1 and WNK4 kinases may play a particular role. The WNK kinases are serine/threonine kinases that were implicated in a variety of functions in the body [4, 54]. The relevance of these kinases for the renal control of Na^+ and K^+ balance and blood pressure is evidenced by the fact that mutations in WNK1 and WNK4 cause familial hyperkalemic hypertension (FHHT) (e.g., [54, 127] and see above). A great body of experimental evidence suggests that the kidney-specific short isoform of WNK1 (KS-WNK1) and the ubiquitously expressed long isoform of WNK1 (L-WNK1) act together with WNK4 in a complex cascade. KS-WNK1 antagonizes the inhibitory effect of L-WNK1 on WNK4 [5, 54, 110]. In this concept, the balance between KS-WNK1 and L-WNK1 and the activity mode of WNK4 are decisive for the control of ion-transporting proteins in the distal tubule including NCC, ROMK, and ENaC and hence for the physiological adaptation of the DCT, CNT, and CD to altered dietary K^+ and Na^+ intake [5, 54, 192]. The balance between KS-WNK1 and L-WNK1 appears to be central for the adaptation of the kidney to either a low K^+ or a high K^+ diet. On a low dietary K^+ intake, the ratio of L-WNK1/KS-WNK1 increases [84] and the excess of L-WNK1 is thought to cause an endocytotic retrieval of ROMK [84] and an activation of both NCC [25, 163] and possibly ENaC [201]. The downregulation of ROMK would directly limit K^+ secretion in the distal tubule. The upregulation of NCC would help to minimize K^+ secretion, by reducing the Na^+ and fluid delivery to the downstream localized segments. At the same time, the stimulatory effect of L-WNK1 on ENaC partially counteracts the downregulation of ENaC caused by the suppressed aldosterone levels due to the low K^+ intake. This may promote an inadequately high

Na^+ reabsorption in the ENaC-positive distal tubules contributing to the hypertensive effect of a low K^+ diet [66]. In contrast, a high K^+ diet lowers the ratio of L-WNK1/KS-WNK1 [184] and the increased level of KS-WNK1 should ultimately lead to a stimulation of ROMK [184] and inhibition of NCC [58, 163]. Together with the aldosterone-dependent activation of ENaC, this profoundly favors renal K^+ secretion. L-WNK1 and KS-WNK1 may also contribute to the control of BK activity. Hadchouel et al. observed an enhanced BK α protein abundance in KS-WNK1 knockout mice suggesting a possible regulatory role of KS-WNK1 [58]. However, Cheng et al. did not find any evidence for an altered BK channel activity in collecting ducts of K^+ -loaded KS-WNK1-deficient mice [28]. L-WNK1 was reported to activate BK, which may alleviate L-WNK1-dependent inhibition of ROMK [90].

At the same time, the WNK kinases may also allow to independently adapt renal K^+ and Na^+ excretion and to account for the so-called aldosterone paradox [5]. Both a low Na^+ diet and a high K^+ diet increase plasma aldosterone levels. However, the primary physiological response elicited by aldosterone during dietary Na^+ restriction is renal Na^+ retention, whereas during dietary K^+ loading, the response is kaliuresis [5]. WNK4 was proposed to act as an essential molecular switch between these two states [74, 81]. Under standard conditions, WNK4 inhibits NCC [74, 81, 202], ENaC [139, 206], ROMK [74, 84, 140], and BK [190, 208, 212] activity. During dietary Na^+ restriction, the elevated plasma aldosterone and angiotensin II levels stimulate ENaC activity [92]. The elevated angiotensin II (Ang II) levels do also convert WNK4 to a profound stimulator of NCC [21], which together with the activation of ENaC maximizes renal Na^+ retention. At the same time, angiotensin II seems to stabilize the inhibitory activity of WNK4 on ROMK and thereby to minimize renal K^+ secretion [207]. During dietary K^+ loading, ENaC is also activated via aldosterone, but due to the unchanged angiotensin II levels, WNK4 does not switch from inhibition to activation of NCC [5]. Support for these hypotheses comes from numerous experiments in vitro and in vivo (reviewed in [4, 5, 54, 127, 162, 174, 192]) and the observation that dietary Na^+ and K^+ intake indeed differentially modulate the renal mRNA expression of KS-WNK1, L-WNK1, and/or WNK4 in the expected directions [84, 117, 184]. Likewise, dietary Na^+ and K^+ intake were reported to modulate the protein abundance of WNK4 as well as the abundance and phosphorylation of the downstream-acting kinase SPAK [137, 179, 182]. However, the results were not always consistent, and their interpretation is complicated by the fact that WNK4 and SPAK are expressed in several nephron portions, making analyses on the whole organ level difficult. Moreover, altered dietary K^+ intake may not only change the abundance and phosphorylation but also the subcellular localization of these kinases [179], which may further contribute to the complexity of this signaling pathway. Interestingly, a recent study using

WNK4 knockout and SPAK knock-in mouse models suggested that the regulation of NCC by ANG II but not by dietary K^+ depends on the integrity of the WNK4/SPAK pathway [20], suggesting that the K^+ -induced effects on NCC may involve additional molecular regulators.

The mechanism, by which an altered dietary K^+ intake interferes with the WNK pathway, begins to be unraveled. There is evidence that changes in extracellular K^+ concentration directly affect WNK1 expression and activity [111]. A possible hypothesis for the explanation of such direct effects comes from recent observations in a mouse model for the human EAST/SeSAME syndrome [210]. The EAST/SeSAME syndrome is caused by mutations in the KCNJ10 K^+ channel that is expressed in certain neurons and in the basolateral plasma membrane of the DCT. The patients suffer from epilepsy, ataxia, sensorineural deafness, and a salt-wasting renal tubulopathy that is similar to that seen in patients with Gitelman syndrome [9]. Consistently, KCNJ10-deficient mice reveal a drastically reduced NCC abundance in the kidney [210]. The authors proposed that the loss of the KCNJ10-mediated K^+ conductance depolarizes the cells and decreases the electrochemical driving force for Cl^- to exit across the basolateral ClC -K Cl^- channels. The subsequent increase in intracellular Cl^- concentration would ultimately suppress SPAK and hence NCC activity [210]. Interestingly, recent crystallographic data and mutational analysis suggested that the WNK1 kinase domain comprises a Cl^- -binding pocket. The binding of Cl^- to this site would inhibit the autophosphorylation of WNK1 and thereby its kinase activity [128]. Likewise, Cl^- -binding to a homologous binding pocket in WNK4 may switch this kinase from an activator to an inhibitor of NCC phosphorylation and activity [13]. Thus, WNK1 and WNK4 may act as intracellular Cl^- sensors that indirectly sense changes in extracellular K^+ concentrations. Support for this model comes from recent experimental studies in HEK293 cells which suggested that lowered extracellular plasma K^+ concentrations cause a KCNJ10-dependent hyperpolarization of the plasma membrane. Such depolarization increases Cl^- efflux through ClC -Kb Cl^- channels and finally activates the WNK/SPAK pathway through the lowered intracellular Cl^- concentration [172]. Interestingly, WNK4 knockout mice and a knock-in mouse model expressing a mutant form of SPAK that cannot be activated via WNK4 still respond to a dietary K^+ load with reduced NCC phosphorylation [25]. These evidences suggest some redundancy in the signaling mediating the effect of altered dietary K^+ on NCC.

Conclusion

As outlined in this review, there are numerous complex interactions between dietary K^+ intake and the renal control of Na^+ balance and blood pressure. Since the initial suggestion by

W.L.T. Addison, an impressive body of evidence confirmed the beneficial effect of a high K^+ diet on arterial blood pressure and cardiovascular outcome. Studies in animal models linked part of these effects to the inhibition of renal Na^+ reabsorption, which may involve a rapid inactivation of the thiazide-sensitive NCC in the DCT. This thiazide-like effect of K^+ may not only lower arterial blood pressure but may also improve renal K^+ excretion by increasing Na^+ and fluid delivery to downstream localized tubular segments. In addition to the pronounced effect of dietary K^+ on NCC, the downregulation of other ion transport processes in the nephron also contributes to the natriuretic and antihypertensive effect of a K^+ -rich diet. This may not only include the inhibition of Na^+ transport in the proximal tubule and thick ascending limb but also effects on intercalated cells in the renal collecting system. The role of the latter in blood pressure control is receiving increasing attention, which is further boosted by the recent demonstration that a high K^+ diet modulates the phosphorylation and hence the activity of the mineralocorticoid receptor specifically in intercalated cells [152]. Although the precise physiological impact of this effect remains to be established, the findings further underline the intricate interplay of different renal epithelial cell types in the maintenance of ion homeostasis.

We just started to get insights into the molecular mechanism by which an altered dietary K^+ intake modulates the activity of ion transporting pathways along the renal tubular system. Particular roles appear to play the WNK kinases, which are thought to act as molecular switches, allowing the kidney to independently adapt urinary K^+ and Na^+ excretion to functional needs. Nevertheless, important questions regarding the interaction of these kinases with other signaling pathways in the context of an altered dietary K^+ intake are still unresolved. Moreover, although direct K^+ sensing in adrenal zona glomerulosa has been demonstrated, it remains elusive if and how direct K^+ sensing occurs in the kidney and perhaps in other organs including the gut and by which mechanisms the sensed information is transmitted to the renal epithelia and their various membrane proteins involved in transepithelial Na^+ and K^+ transport. The identification of aldosterone-dependent and independent effects and the characterization of their crosstalk are needed to better understand the complex regulation of K^+ and Na^+ homeostasis and blood pressure control. Eventually, this may help to develop novel strategies to take advantage of the beneficial effects of a K^+ -rich diet that does not only include the antihypertensive effects but also reduced risks for urolithiasis and osteoporosis and an improved glucose tolerance [61].

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